1. (Amended) A synthetic oligonucleotide comprising a contiguous stretch of at least about 15 nucleotides of at least one of SEQ ID NOS:9-13, 15, 17, and 18.

11. (Amended) An isolated polynucleotide capable of hybridizing to a polynucleotide or an oligonucleotide of Claim 1, 3, 4, or 5 under high stringency conditions comprising incubating at 65°C in 0.5M $NaHP0_4$, 7% sodium dodecyl sulfate (SDS), 1mM EDTA and washing at 68°C in 0.1xSSC and 0.1% SDS.

REMARKS

Claims 1, 3, 4, 10, and 11 are pending in the instant application. Applicants submit that Claims 1 and 11 have been amended to particular point out and distinctly claim the subject matter which the inventors regard as the invention. The amendments are fully supported by the specification and claims as originally filed. The amended claims are supported in the specification, *inter alia*, at page 13, lines 24-28; and page 16, lines 1-30.

I. THE INVENTION

The present invention relates, in part, to oligonucleotides and polynucleotides that are discovered using gene trap technology. The gene trap vectors used in the invention can integrate into intron sequences of cellular genes. The cellular genes in which the vector are inserted (the "trapped genes") may be cloned easily since the vectors are designed such that fusion transcripts are formed with the trapped genes. The fusion transcripts comprise exon sequences of the trapped gene appended to a selectable marker that facilitates isolation by polymerase chain reaction-based protocols or by cDNA cloning. In some cases, integration disrupts the transcription of the trapped gene and results in a null mutation at the locus. In this application, the claimed invention relates to oligonucleotides and polynucleotides comprising the disclosed polynucleotide sequences of SEQ ID NOS:9-18 which are trapped genes obtained from human teratocarcinoma cells.

II. THE REJECTION UNDER 35 U.S.C. § 101 IS IN ERROR

Claims 1, 3, 4, 10, and 11 are rejected by the Examiner under 35 U.S.C. § 101 as allegedly lacking patentable utility for the lack of a specific, substantial, and credible utility. Claims 1, 3, 4, 10, and 11 recite oligonucleotides or polynucleotides comprising the

disclosed polynucleotide sequences of SEQ ID NOS:9-18. Applicants respectfully traverse the rejection on the ground that such oligonucleotides or polynucleotides have specific, substantial, and credible utilities as described in the specification.

The Examiner states that the claimed nucleic acid lacks specific utility because the nucleic acids are not disclosed as being useful as a probe for detecting a specific clinical condition. Applicants submit that it is not necessary to show that a probe can detect a specific clinical condition in order to satisfy the specific utility requirement. The Examiner further states that simply stating that a nucleic acid could be used as a probe, primer, or anything, does not constitute a specific utility because any piece of nucleic acid would invariably hybridize to another piece of nucleic acid. Applicants submit that the claimed oligonucleotides or polynucleotides of the present invention is not just any piece of nucleic acid.

According to the Examination Guidelines for the Utility Requirement, if the applicant has asserted that the claimed invention is useful for any particular practical purpose (*i.e.*, it has a "specific and substantial utility") and the assertion would be considered credible by a person of ordinary skill in the art, the Examiner should not impose a rejection based on lack of utility (66 FR1098 January 5, 2001). A description of specific utility may be found in the Revised Interim Utility Guidelines Training Materials. Specific utility is:

> "a utility that is specific to the subject matter claimed. This contrasts with a general utility that would be applicable to the broad class of the invention. For example, a claim to a polynucleotide whose use is disclosed simply as a "gene probe" or "chromosome marker" would not be considered to be specific in the absence of a disclosure of a specific DNA target. Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed." (http://www.uspto.gov/web/menu/utility).

Unlike the example cited in the above definition where any fragment of genomic DNA can in theory be used as a probe or a chromosome marker, the polynucleotide sequences of SEQ ID NOS:9-18 has specific utility.

According to the invention, gene trap vectors were introduced into human teratocarcinoma cells which result in the identification of the gene loci that comprise the sequences set forth in SEQ ID NOS: 9-18. After the gene trap vector had integrated nonspecifically into the human teratocarcinoma cell genome, fusion transcripts were

expressed. Each fusion transcript comprises exons that are located either upstream or downstream from the integration site. These exons, which are portions of a genetic locus that was disrupted by a gene trap vector, were cloned and represented by the presently claimed oligonucleotides and polynucleotides.

The genetic loci, as represented by the presently claimed oligonucleotides or polynucleotides, which have been disrupted in the teratocarcinoma cells fall within a specific class of genes which are distinct from the broad general class of genes in the genome. Applicants point out that these genetic loci encode genetic functions which are not involved in the general survival, *i.e.* house-keeping functions, of teratocarcinoma cells and that both copies of functional allele at these loci are not required for survival. The teratocarcinoma cells, after transfection with the gene trap vectors, survived and propagated with only one non-disrupted allele of the genetic loci. These genetic loci and the products encoded by these loci are essentially preselected by the transfection for possessing functions that are specifically involved in the differentiation and development of such cells.

Applicants submit that the present invention can be used to identify and study genes that are involved in the late stages of stem cell differentiation and development. This is due to the unique nature of teratocarcinoma cells which are "stem cells" that occur in unusual germ cell tumors. Stem cells are defined by the ability both to produce identical daughter cells (self-renewal), and to produce progeny with more restricted fates (commitment and differentiation). This property of stem cells underpins growth and diversification during development and sustains homeostasis and repair processes throughout adult life. An understanding of molecular mechanisms which govern stem cell fate is therefore of fundamental significance in cell and developmental biology and the capabilities arising from such knowledge have major biomedical applications.

In many ways, teratocarcinoma cells resemble normal embryonic stem cells and represent a good model for molecular mechanisms of embryonic development and differentiation. Applicants submit that genes that are critically essential to the survival of teratocarcinoma cells would not have been isolated and propagated by the gene trap methods of the invention, and would likely have been eliminated after the transfection with gene trap vectors. Thus, the sequences set forth in SEQ ID NOS: 9-18 represent a sample of genetic sequences that may play a role in late stages of stem cell differentiation and development. Accordingly, the utility of these sequences are not general and are not shared by any random

pieces of genomic DNA. Not every gene in the genome necessarily provide this specific utility of the oligonucleotides and polynucleotides of the invention. Thus, Applicants submit that the claimed oligonucleotides and polynucleotides have specific utility.

The Examiner further states that in order to have substantial utility, hybridization of a nucleic acid has to infer useful information. Applicants submit that these genetic loci as represented by the presently claimed oligonucleotides or polynucleotides have substantial utility because they provide useful information regarding gene expression in teratocarcinoma cells which mimics gene expression during the late stages of stem cell differentiation and development.

Applicants submit that the claimed oligonuceotides and polynucleotides can be used as probes in hybridization assays well known in the art to determine the activity at the genetic loci during development and differentiation of the teratocarcinomas (See for example, page 41, line 3 to page 42, line 6). Teratocarcinomas are totipotent which means that they may be differentiated into many different cell types (such as teeth, hair, bone, muscle and cartilage) along various pathways upon induction by certain signals. Each of these pathways may require expression of one or more genes that are disclosed in the specification as filed and represented by the presently claimed oligonucleotides and polynucleotides. Thus, the claimed oligonucleotides and polynucleotides can be used as probes, for example, in Northern blot analysis (page 41, lines 12-15), or in situ hybridization (page 41, lines 7-11), for undifferentiated teratocarcinomas or differentiated teratocarcinomas of different lineages or at different stages of differentiation and development. The expression pattern of each of these genes can thus be correlated with known events that occur in particular stages of development and cell differentiation. As such, the utility is substantial and credible in a real world context.

The above described techniques are well known in the art and hence utilities of the present invention are credible. As stated in the Examination Guidelines for the Utility Requirement, credibility is assessed from the perspective of one of ordinary skill in the art in view of the disclosure or any other evidence of record. Furthermore, the Revised Interim Utility Guidelines Training Materials states that assertion of utility is credible if it is believable to a person of ordinary skill in the art based on the totality of evidence and reasoning provided. Accordingly, not only do the oligonucleotides and polynucleotides of the present invention have specific utilities, their utilities are credible and practical.

In view of the foregoing, Applicants submit that the claimed invention has specific, substantial and credible utility.

III. THE REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH SHOULD BE WITHDRAWN

Claims 1, 3, 4, 10, and 11 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking utility. Applicants traverse this rejection on the ground that Claims 1, 3, 4, 10, and 11 have significant patentable utility as discussed in Section II, above. Applicants submit that when an Applicant satisfactorily rebuts a rejection based on a lack of utility under 35 U.S.C. § 101, the corresponding rejection imposed under 35 U.S.C. § 112, first paragraph, should also be withdrawn. Thus, Applicants respectfully request that the rejection of Claims 1, 3, 4, 10, and 11 under 35 U.S.C. § 112, first paragraph, be withdrawn.

Claims 1, 3, 4, 10, and 11 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter that was not described in the specification. The Examiner states that the specification does not describe a clear length of an oligonucleotide. The Examiner states:

> it was not apparent from the specification that claimed SEQ ID Numbers contain a complete open reading frame. . . . would read on undiscovered genes and nucleic acid sequence from other species, allelic variants, and so forth which are clearly not described by the disclosure of the instant application as such sequence would comprise the claimed SEQ ID Numbers. If the SEQ ID Numbers claimed by Applicant do contain complete open reading frames, and evidence is provided, the rejection will be withdrawn.

Applicants traverse this rejection on the ground that identification of the complete open reading frames is not necessary to satisfy the description requirement under 35 U.S.C. § 112, first paragraph. Claims 1, 3, 4, 10, and 11 indeed are fully supported by the specification and claims as originally filed.

35 U.S.C. § 112, first paragraph, requires that the specification contain a written description of the invention. An applicant must convey with reasonable clarity to those skilled in the art that the applicant was in possession of the invention. Vas-Cath v. Mahurkar, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). "The written description must communicate that which is needed to enable the skilled artisan to make and use the claimed

invention." Kennecott Corp. v. Kyocera Int'l, Inc., 835 F.2d 1419, 1421, 5 U.S.P.Q.2d 1194, 1197 (Fed. Cir. 1987), cert. denied, 486 U.S. 1008 (1988).

Moreover, according to the Guidelines for Examination of Patent Applications Under the 35 U.S.C. § 112, ¶ 1, "Written Description" Requirement (Federal Register v. 66, no. 4, pages 1099-1111, January 5, 2001, the "Guidelines"), the written description requirement may be satisfied by disclosure of relevant, identifying characteristics, *i.e.*, structure or other physical or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus.

Claims 1, 3, 4, 10, and 11 recite synthetic oligonucleotides or isolated polynucleotides corresponding to one of SEQ ID NOS:9-18. The synthetic oligonucleotides or isolated polynucleotides are fully described by *structure* or by *physical properties*, or both, sufficient to distinguish the claimed synthetic oligonucleotides or isolated polynucleotides from other materials. For instance, Claim 1 recites synthetic oligonucleotides that comprise a contiguous stretch of at least about 15 nucleotides of at least one of SEQ ID NOS:9-13, 15, 17, and 18. As the exact structure of SEQ ID NOS: 9-13, 15, 17, and 18 are provided in the specification, although there are numerous oligonucleotides that falls within this description, one person of skilled in the art can make the synthetic oligonucleotide as described in claim 1. Likewise, Claim 11 describes a genus of polynucleotides by a property (i.e., hybridizable under defined conditions to known sequences) that readily distinguishes the claimed polynucleotides from other materials. One of skill in the art can readily isolate the claimed polynucleotides of Claim 11 and distinguish it from other polynucleotides by performing a hybridization as recited in the claim.

Applicants respectfully point out that the chemical structure of the claimed genus of nucleic acid molecules are described and well known in the art (e.g., DNA, RNA) and that the variation of nucleotide sequence within the claimed genus is also well defined by the functional characteristics of specifically binding under defined hybridizing conditions to nucleic acid molecules of known sequences. See footnote 42 of the Guidelines wherein it is stated that examples of identifying characteristics include a sequence, structure, binding affinity, binding specificity, molecular weight, and length, and also detailed restriction enzyme maps, antibody cross-reactivity, unique cleavage by particular enzymes. One of skill

in the art would recognize from the combination of identifying structural and functional characteristics disclosed in the specification that Applicants have possession of the claimed genus of nucleic acid molecules. In fact, the skilled person can readily recognize and determine whether a nucleic acid molecule falls within the pending claims by either comparing the sequence of the molecule with the sequences provided in the application and/or performing a hybridization reaction under defined conditions with the nucleic acid molecule(s) described in the present application. As such, Applicants submit that adequate written description has been provided.

The Examiner alleges that it was not apparent from the specification that claimed SEQ ID Numbers contain a complete open reading frame and that the claimed subject matter would read on undiscovered genes and nucleic acid sequence from other species, allelic variants, and so forth which are clearly not described by the disclosure of the instant application as such sequence would comprise the claimed SEQ ID Numbers. Applicants submit that the specification discloses exemplary elements that may be included in the claimed oligonucleotides or polynucleotides, such as non-coding or regulatory regions (page 23, lines 13-20); vector sequences (page 23, lines 3-8), other coding sequences as obtained by "primer extension" (page 10, lines 18-23). As such, the specification is replete with description of representative elements that may be included in the claimed oligonucleotides and polynucleotides. Applicants submit that the written description requirement for the claimed genus of molceules are met.

In view of the foregoing, Applicants respectfully request that the rejection of Claims 1, 3, 4, 10, and 11 under 35 U.S.C. § 112, first paragraph, be withdrawn.

IV. THE REJECTIONS UNDER 35 U.S.C. § 102(b) SHOULD BE WITHDRAWN

Claims 1 to 2 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Adams *et al.*, 1997 ("Adams *et al*"). Since claim 2 has been canceled, rejection with respect to this claim is rendered moot. The Examiner states that Adams et al. discloses a nucleic acid sequence which comprises at least about contiguous 15 contiguous nucleotide sequence to that of *SEQ ID NO:13*. Applicants submit that Adams et al. teaches the following sequence:

```
ggacagtggc taactcagca gacgaaccag agcttcatgc cctttgcaga tggcatgaag 60
ataagagttt gccaaacaac taagatgggc tcttgattga gcaaagaaac cacaacatgg 120
gacacacaga gccacctaat tgccatactg tcattcaagc ttaaaggaga catatctaca 180
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gacagggttt gagcatagta atggtgagaa ctttcttgga tgtctcaaca gcctggagat 240
gaaattccca agaaggcaga aaatagaggt ggcacattgg ttttattgtt ttttattaca 300
attataaaag taatgcatgc tttttgt                                     327
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The sequence of SEQ ID NO:13 is:

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tggtgcttac taaaaattga ataancgtgg aaaagagaaa atctccctct ttaaaaggaa 60
cactgttgtg gacattttaa aatgcaaacg ccttggctgg aagtcagaaa tcgtgttctc 120
tctgctaaac ctggtgtagc atttaacacg cttgaagtgg aggcatctgg tcaccaattt 180
cacagcctgg acagagcaag aaggtgcggc tggcttagga ggcggcctgc cgggggggat 240
cgtctgtcca tctgggcttg gtaaatgtca agggtcattt ccctgtcctg acatttgatt 300
gtgaagcagg ttgcgaggta actctttcaa gggactggac tgtgacagtc accatagttg 360
gacaataaaa cccgaacatc cttcacc                                     387
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As such, Applicants submit that there is in fact no homology between SEQ ID NO:13 and Adams et al. Thus, Adams et al. does not teach or suggest Claim 1. Applicants request that the rejection of Claim 1 under 35 U.S.C. § 102(b) is in error and should be withdrawn.

CONCLUSION

Applicants submit that Claims 1, 3, 4, 10 and 11 satisfy all of the criteria for patentability and are in condition for allowance. An early indication of the same and passage of Claims 1, 3, 4, 10, and 11 to issuance is therefore kindly solicited.

Respectfully submitted,

By: [signature] 40,258

Date: January 3, 2002

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Exhibit A
Marked-Up Version of Amended Claims

1. (Amended) A synthetic oligonucleotide comprising a contiguous stretch of at least about 15 nucleotides of at least one of SEQ ID NOS:9-13, 15, 17, and 18.

11. (Amended) An isolated polynucleotide capable of hybridizing to a polynucleotide or an oligonucleotide of [Claims] Claim 1, 3, 4, or 5 under high stringency conditions comprising incubating at 65°C in 0.5M $NaHP0_4$, 7% sodium dodecyl sulfate (SDS), 1mM EDTA and washing at 68°C in 0.1xSSC and 0.1% SDS.

Exhibit B
Pending Claims

1. (Amended) A synthetic oligonucleotide comprising a contiguous stretch of at least about 15 nucleotides of at least one of SEQ ID NOS:9-13, 15, 17, and 18.

3. (Amended) An isolated polynucleotide comprising a contiguous stretch of at least about 60 nucleotides of at least one of SEQ ID NOS:9-18.

4. (Amended) An isolated polynucleotide according to Claim 3, wherein said polynucleotide sequence comprising at least one of SEQ ID NOS:9-18.

10. (Amended) A synthetic oligonucleotide comprising a contiguous stretch of at least about 20 nucleotides of at least one of SEQ ID NOS:16.

11. (Amended) An isolated polynucleotide capable of hybridizing to a polynucleotide or an oligonucleotide of Claim 1, 3, 4, or 5 under high stringency conditions comprising incubating at 65°C in 0.5M $NaHP0_4$, 7% sodium dodecyl sulfate (SDS), 1mM EDTA and washing at 68°C in 0.1xSSC and 0.1% SDS.